Author's response to reviews

Title: A meta-analysis of the performance of the PimaTM CD4 for point of care testing

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Version: 3 Date: 12 May 2015

Author's response to reviews: see over
Dr Lin Lee  
Deputy Editor  
BMC Medicine  
11th May 2015  

Dear Dr Lee  

Re-submission of a manuscript titled “A meta-analysis of the performance of the PIMA CD4 for point of care testing”  

Thank you for this opportunity to re-submit our manuscript with improvements. We have addressed the reviewer’s comments as itemized below and tracked changes in the document.  

Response to reviewer’s comments.  
I would suggest that you expand your discussion to elaborate on the importance of your study in response to Reviewer 2’s comments  

Reviewer 2: The issues which could be raised are the following:  

The decreasing place of CD4 T cell count in developing countries for HIV monitoring. According to the new WHO (2013-revised) guidelines, the best marker to monitor HIV infection in resource-limited settings is currently the HIV(RNA) load, no more the CD4 T cell count. The only interesting (meaning operational) threshold evaluated by the authors is the CD4 T cell threshold to initiate the antiretroviral treatment (e.g. 500 CD4 cells/ml); the others thresholds (e.g. 100 or 350) are much less interesting to be considered.  
The meta-analysis shows clearly that around 10% of patients are in fact misclassified. The conclusion stating that "Pima CD4 for HIV ART eligibility at 500cells/µl threshold" should be obviously attenuated. In Western countries, the Pima assay would have been abandoned; thus it is OK for developing countries  

1. The authors thank this reviewer for their critical question; however it has been addressed in the discussion. Although the reviewer feels that 10% misclassification is unacceptable (irrespective of the developed or developing world), this is misunderstood by the reviewer. It shows that this 10% is the total misclassification, which is made up of 7% false positivity. This means 7% patients are eligible for treatment (and therefore acceptable) if using Pima sooner than reference technology, this therefore is to the benefit of patients, and only 3% would be missed. The impact therefore on using Pima in either developed or developing world is therefore more on the cost of providing more treatment sooner. This is already stated in the discussion (yellow highlight, Page 20 of the discussion) and does address this query of the reviewer, to clearly show the benefit to patients.  

“Programmatic implications are important to consider when implementing a new testing technology, and these increased false positive and downward misclassification rates mean that more patients will be identified as eligible for treatment. While this will lead to initial increases in
overall program costs, treatment is initiated sooner with greater impact on patient’s life years saved [14,16,17,31,32]”.

2. The issue about the threshold of 500cells/µl being the only interesting threshold based on recent guidelines is appreciated for ART initiation, yet many countries have not adopted this level yet, and the authors feel the inclusion of analysis at the 100cells/µl and 350cells/µl threshold is important. Moreover at 100 cells/µl, where there is a need for reflex testing for Cryp Ag screening (and therefore highly relevant operationally), which has never been reported before in the context of POC CD4 testing, and where significant differences are shown between specimen types is highly relevant. An additional statement has however been added to ensure focus on the 500cells/µl threshold.

“It is worth stressing that these implications apply across the different thresholds irrespective of the changes in treatment guideline to the 500cells/µl threshold”.

The authors wish themselves to make additional corrections, which are highlighted and stated below:

1. Three co-authors that are part of this study are from the CDC, and hence where awaiting CDC internal approval before publication. This has now been granted, and we would like to add these co-authors as tracked in the text.
2. One modification to the title requested by the CDC is to change the word “continent” to “5 regions”. This is also highlighted.

**Reviewer 1:** Minor essential revisions
1. It would be helpful if some of the statistics were better explained so we understand why they are included. What is the difference between false positives/negatives and upward/downward misclassifications. They seem like the same thing.
2. Why is percent similarity used in addition to percent bias? Differences from 1 do not seem as large as differences from 0, although they both may be significant.
3. On the other hand, why were NPV and PPV calculations not included?
4. It would be helpful if the authors summarized all the measures that lead them to their conclusions. The strength of the report is the multiple ways in which performance was measured. The weakness is in explaining how they came to their conclusions.

The authors feel all these comments are sufficiently described and further detail would detract from the main conclusions. All statistical methods applied are well referenced for readers to further investigate for more details.

**Major compulsory revisions** – errors in interpretation
5. The authors’ conclusions as to the clinical acceptability of their findings are questionable, and are not supported by referenced cost-effectiveness or outcome evidence. What is the basis for making the statement that “The Pima CD4 may be recommended using venous-derived specimens for screening (100cells/µl) for reflex CrAg screening; and for HIV ART eligibility at 350cells/µl and 500cells/µl thresholds using both capillary and venous derived specimens.” Some of the measures, like a misclassification rate of 9%, with a false positive rate of 6% might be very costly. Screening tests should, in general, have excellent specificity, and numbers less than 90% would be judged problematic regions with low HIV prevalence.
The issues around cost effectiveness are not addressed in this meta-analysis, and this is so stated in the opening abstract.

6. Why did the authors conclude that venous blood was acceptable but capillary blood was not? Where does one draw the line between specificities of 89 and 82%? Why not draw the line at 90%?

The authors feel there is sufficient information to address this query, with extensive information provided with confidence intervals and follow up with clinical relevance.

Yours sincerely

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